Aging Neuroscience: Udall Center for Excellence in Parkinson Disease

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on behalf of Ray Dorsey, MD, MBA

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Delmonte Institute for Neuroscience Retreat
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Vision: To enable anyone, anywhere, to participate in research, benefit from therapeutic advances, and receive care.
Drug development productivity is declining; new methodological models are needed

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>20th Century</th>
<th>21st Century</th>
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<tbody>
<tr>
<td>Study design</td>
<td>Randomized, double-blind, parallel-group, placebo-controlled trial</td>
<td>Randomized, double-blind, parallel-group, placebo-controlled trial using adaptive designs</td>
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<tr>
<td>Study population</td>
<td>All comers with a given disease</td>
<td>Individuals selected based on phenotypic and genetic results</td>
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<tr>
<td>Study recruitment</td>
<td>Clinical practices</td>
<td>Global clinical trial registries and social networks organized by individuals affected by the disease</td>
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<tr>
<td>Trial visits</td>
<td>In person and audio calls</td>
<td>In person and audio and video calls</td>
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<tr>
<td>Data management</td>
<td>Paper and electronic forms</td>
<td>Electronic forms</td>
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<tr>
<td>Participant feedback</td>
<td>Limited, delayed</td>
<td>Almost universal, approximately real time</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>Insensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td></td>
<td>Episodic</td>
<td>Frequent or continuous</td>
</tr>
<tr>
<td></td>
<td>Subjective</td>
<td>Objective</td>
</tr>
<tr>
<td></td>
<td>Provider centered</td>
<td>Patient centered</td>
</tr>
<tr>
<td></td>
<td>In clinic</td>
<td>Remote</td>
</tr>
<tr>
<td></td>
<td>Unidimensional</td>
<td>Multidimensional</td>
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</table>

Udall Centers define the causes of and discover improved treatments for Parkinson disease

Udall Centers – at a glance

**Background:** Funded by Morris K. Udall Parkinson’s Disease Research Act of 1997 in honor of long-serving Representative Morris Udall, who had PD

**Goal:** “To rapidly advance synergistic, interdisciplinary research programs while serving as national leaders in PD research.” Stated theme will “inform the etiology, pathogenesis, or treatment of PD”

**Centers:** 9 nationwide

**Required components:**
- Administrative Core
- At least one integrated Research Core to support at least two research projects
- At least three Research Projects
- Mission statement
- Plan for periodic outreach activities
- Clinical research core if at least one Clinical Research Project is proposed

Source: RFA-NS-16-002
In the P20 planning grant, we outlined three research projects

Proposed transition from P20 to Udall Center Research Projects

<table>
<thead>
<tr>
<th>Exploratory (P20) Research Projects</th>
<th>Udall Center (P50) Research Projects</th>
<th>Tools for PD Clinical Research</th>
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</thead>
<tbody>
<tr>
<td><strong>Aim 1</strong>: Develop a predictive model of PD progression</td>
<td><strong>Project 1</strong>: Application of modeling and simulation methods to existing PD clinical data</td>
<td>In silico models that predict PD progression and inform clinical trial design</td>
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<tr>
<td><strong>Aim 2</strong>: Pilot software for remote assessment of PD</td>
<td><strong>Project 2</strong>: Evaluate technologies for remote assessment of PD patients and research participants</td>
<td>Validated approach and technology for conducting remote assessments</td>
</tr>
<tr>
<td><strong>Aim 3</strong>: Pilot smart phone application for remote assessment of PD</td>
<td><strong>Project 3</strong>: Evaluate novel technologies to objectively measure PD features</td>
<td>Novel, objective continuous measures of PD</td>
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</table>
Developing Predictive Models of PD Progression

• Reverse Engineering and Forward Simulation (REFS™) to generate prediction models for progression
  – Uses Bayesian inference, modeling directly from data without pre-specified hypotheses
  – Produces ensemble of models sampled from the Bayesian posterior

• Three outcomes (rate of progression) modeled separately
  – Motor (MDS-UPDRS Parts II and III)
  – Cognition (MoCA)
  – Functional and Behavioral (MDS-UPDRS Part I)
Predictors to be evaluated for the longitudinal endpoints of interest

<table>
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<tr>
<th>Cohort</th>
<th>Clinical Variables</th>
<th>Genotyping</th>
<th>Endpoints</th>
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</table>
| PD (Including SWEDD patients) N=241 | **Demographics**
  Age, Gender, Race, Ethnicity, Education

**Medical History**
Family history of PD, PD medication use, Tremor-dominance, Primary affected side, REM sleep disorder

**Baseline Clinical Tests**
DATScan imaging, Evidence of dopaminergic deficit (SWEDD flag), UPSIT

**Baseline Levels of Disease Severity**
Montreal Cognitive Assessment (MoCA), MDS-UPDRS

**Baseline CSF Protein Tests**
β-amyloid1-42, α-synuclein, Total tau, Phosphorylated tau 181 | **ImmuNoChip**
Illumina Infinium iSelect HD Custom Genotyping array | Rate of decline across 3+ years of follow-up
Cognitive: Montreal Cognitive Assessment (MoCA) (N=345)
Motor: MDS-UPDRS, Part II & III (N=333)
Functional & Behavioral: MDS-UPDRS, Part I (N=333) |
Testing the feasibility of Virtual Visits

Pilot randomized, controlled study of telemedicine for Parkinson disease

4 nursing home residents with PD

3 telemedicine visits over 6 months

“Usual care” for 6 months

10 individuals from the local community with PD

3 telemedicine visits over 6 months

Outcomes

Primary outcome
• Feasibility as measured by proportion of telemedicine visits completed as scheduled

Secondary outcomes
• Reliability and validity of the UPDRS motor examination
• Quality of life
• Patient satisfaction
• Motor performance
• Mood
• Cognition

Telemedicine visits were feasible
Remote assessment of the UPDRS was reliable
(remote v in-person ICC 0.78; test-retest remotely ICC 0.82)

A modified UPDRS conducted remotely is cross-sectionally and longitudinally valid.

![Graph](image)

**Fig. 1.** Scatter plots for (A) modified motor UPDRS (mUPDRS) versus standard motor UPDRS at baseline, (B) mUPDRS versus UPDRS at 2-year follow-up, and (C) change from baseline to 2-year follow-up for mUPDRS versus UPDRS. Solid lines represent best-fit linear regression line (plots A and B) and line of identity (plot C). For plots A and B, dashed line represents 95% confidence interval and dotted line represents 95% prediction interval about the best-fit line.
REACT-PD Study Design

• Observational study assessing feasibility of conducting virtual research visits in a subset of individuals with early PD participating in an ongoing clinical trial (STEADY-PD III)
• 40 participants in STEADY-PD III who consented to be contacted for future research will be enrolled and followed for up to 12 months
• Virtual Research visits to occur within 4 weeks after in-person clinical trial visit
• Virtual research visits will collect the same data as is collected at the corresponding in-person visit and include:

<table>
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<tr>
<th>Every Visit</th>
<th>Annual Visit Only</th>
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<tr>
<td>UPDRS I-IV*</td>
<td>MDS UPDRS</td>
</tr>
<tr>
<td>Hoen and Yahr</td>
<td>MoCA</td>
</tr>
<tr>
<td>Schwab and England ADL</td>
<td>PDQ-39</td>
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<tr>
<td>C-SSRS</td>
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<tr>
<td>Concomitant medications</td>
<td></td>
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<td>Evaluate need for therapy</td>
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<td>Participant/investigator surveys</td>
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*Primary outcome measure of STEADY-PDIII
Software applications for remote measurement

Pilot smartphone study in Parkinson disease

DFA = detrended fluctuation analysis; TKEO = Teager-Kaiser energy operator

Source: Parkinsonism & Related Disorders 2015 Jun;21(6):650-3
These apps can detect responses from dopaminergic medications

Tapping frequency in individual with PD before and after medication

Source: Sage Bionetworks
Progress and Future Directions

Developing predictive models of PD progression
- Platform for integrated trial datasets
- Identifying influential factors in disease progression
- Validation with external datasets

Testing the feasibility of virtual visits
- Incorporation into trials (STEADY-PD)
- Independent sample – evaluate influence on recruitment, retention

Developing and testing applications for remote measurement
- Incorporate applications into trials (SURE-PD3)
- Pilot wearable sensors for outcome quantification

Future: Incorporate these approaches as a standard in therapeutic development and expand to new disease models